REMARKS

Claims 3-8, 17 and 57-66 are pending. The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry.

35 U.S.C. 112 – Definiteness

Claims 3-8, 17 and 57-66 were rejected under Section 112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants traverse.

The Examiner alleged on page 3 of the Office Action that "the disclosure does not sufficiently describe the structure of the conjugate of fragments and derivatives." He contends that "it is unclear how a fragment can be anything but 100% identical to a sequence" and he noted that "fragments 'are collections of the whole, but are none the less [*sic*] 100% identical to a sequence" (page 2 of the Office Action). With respect to derivatives, the Examiner contends, "Derivatives are post translated modifications to sequences" (*id.*). He suggested "disclosing variants of the polypeptides that have 90% sequence identity" and "separating derivatives from variants to encompass the fragments, variants and derivatives that are conjugated" (*id.*).

Without conceding the propriety of the rejection, Applicants amend the claims to refer to variants of a polypeptide, wherein those variants are at least 50 amino acids and have at least 90% sequence identity to a sequence within the corresponding protein and fragments of a protein, wherein those fragments are at least 50 amino acids and have at least 90% sequence identity to a sequence fragment within the corresponding protein. Applicants' disclosure explains, *inter alia*, at paragraph [0096] et seq. that the present invention relates not only to the specific protein sequences disclosed in the specification, but also to protein variants thereof, such as fragments and derivatives. A variant of a sequence preferably retains at least one biological function or activity of the specific protein sequence, e.g., the ability to be ubiquitylated via the N-end rule pathway or the ability to act as a substrate for a protease that exposes an N-degron.

Moreover, at paragraph [0097], the specification explains that variants of the polypeptides of the invention may be (i) one in which one or more of the amino acid

residues are substituted with a conserved or non-conserved amino acid residue, (ii) one in which there are one or more modified amino acid residues, e.g., residues that are modified by the attachment of substituent groups, (iii) one in which the polypeptide is an alternative splice variant of the polypeptide of the present invention, (iv) fragments of the polypeptide and/or (v) one in which the polypeptide is fused with another polypeptide, such as a leader or secretory sequence or a sequence which is employed for purification or visualization. The fragments include polypeptides generated via proteolytic cleavage (including multi-site proteolysis) of an original sequence. Variants may be post-translationally or chemically modified.

At paragraph [0098], "similarity" between two polypeptides is determined by comparing the amino acid sequence and its conserved amino acid substitutes of one polypeptide to a sequence of a second polypeptide. Variants include polypeptide sequences different from the original sequence, preferably different from the original sequence in less than 40% of residues per segment of interest, more preferably different from the original sequence in less than 25% of residues per segment of interest, more preferably different by less than 10% of residues per segment of interest, most preferably different from the original protein sequence in just a few residues per segment of interest and at the same time sufficiently homologous to the original sequence to preserve the functionality of the original sequence and/or the ability to ubiquitylate via N-end rule pathway. The present invention includes protein sequences that are at least 60%, 65%, 70%, 72%, 74%, 76%, 78%, 80%, 90%, or 95% similar or identical to an amino acid sequence selected from a group listed in Table 1.

The Examiner asserted that it is unclear how a fragment can be anything but 100% identical to a sequence. Moreover, he seemingly considers fragments to be defined as "collections of the whole, but are none the less [sic] 100% identical to a sequence" (page 2 of the Office Action). Applicants cannot agree. It would be understood by the skilled artisan that like a full sequence protein or polypeptide, a fragment or derivative can be less than 100% identical to a given sequence. As described in the specification, variants, e.g., fragments and derivatives, include sequences <u>different</u> from the original sequence.

Moreover, the Examiner appears to be interjecting definitions of limitations used in the claims without considering the guidance provided in the specification. This is improper. The pending claims must be "given their broadest reasonable interpretation consistent with the specification." *Phillips v. AWH Corp.*, 415 F.3d 1303, 75 U.S.P.Q.2d 1321 (Fed. Cir. 2005); *In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359, 1364, 70 U.S.P.Q.2d 1827 (Fed. Cir. 2004). This means that the words of the claim must be given their plain meaning unless the plain meaning is inconsistent with the specification. *In re Zletz*, 893 F.2d 319, 321, 13 U.S.P.Q.2d 1320, 1322 (Fed. Cir. 1989) (discussed below); *Chef America, Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1372, 69 U.S.P.Q.2d 1857 (Fed. Cir. 2004). It is the use of the words in the context of the written description and customarily by those skilled in the relevant art that accurately reflects both the "ordinary" and the "customary" meaning of the terms in the claims. *Ferguson Beauregard/Logic Controls v. Mega Systems*, 350 F.3d 1327, 1338, 69 U.S.P.Q.2d 1001, 1009 (Fed. Cir. 2003).

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

35 U.S.C. 112 – Written Description

Claims 3-8, 17 and 57-66 were rejected under Section 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants traverse because the specification teaches a representative number of species of the claimed genus. The structure of the conjugate after N-end rule ubiquitylation is also clear.

The M.P.E.P. clearly states that a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116 (Fed. Cir. 1991). The applicant shows possession of an invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a

variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 68, 119 S.Ct.304, 312, 48 U.S.P.Q.2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 U.S.P.Q.2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 U.S.P.Q.2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "**whatever characteristics sufficiently distinguish it**"). M.P.E.P. § 2163(I) (emphasis added).

The structure of the claimed conjugates is sufficiently described in the present disclosure to enable the skilled artisan to envisage the members of the genus. First, the complex comprises at least one ubiquitin or a derivative thereof and a protein selected from the group consisting of aprataxin, tau, SLP, HMG17, PinX1, CIR, Cullin 3, HMGN3, HSPC144, CDC6, and variants thereof. The sequences of these proteins are disclosed in Applicants' specification (SEQ ID NOS: 1-12 and Table 1). Moreover, the present specification explains that ubiquitin ligase has been shown to ubiquitylate N-end rule substrates, such as these proteins, and ubiquitin ligase has two binding sites for primary destabilizing N-terminal residues. The type I site is specific for basic N-terminal residues Arg, Lys, His and the type II site is specific for bulky hydrophobic residues, Phe, Leu, Trp, Tyr and Ile.

For example, at paragraphs [0092]-[0095], the specification provides a number of non-limiting examples of sequences that may be used in the constructs of the present invention. For example, certain "activated fragments" may be used, e.g., fragments having an exposed N-degron that is hidden in the whole protein. In one embodiment, the sequence is a C-terminal fragment of protein which is the result of a specific proteolytic cleavage at a site which exposes a destabilized N-terminal residue, e.g., a destabilizing Ile, Glu, His, Tyr, Gln, Asp, Asn, Phe, Leu, Trp, Lys, Arg, Ala, Ser, Thr or Cys, e.g., a destabilizing Glu, Gln, Cys, Arg, Lys, His specific to Type I N-end rule substrate, Leu, He, Tyr, Phe, Trp specific for Type II substrate and Ala, Ser and Thr specific for Type III substrate. The activated fragment may be subjected to additional

proteolysis from the C-terminus either preceding or following a cleavage event which exposes an N-degron. Examples of such sequences are provided in the specification and are excerpted below:

- Activated fragments of aprataxin include an approximately 2021.5 kDa C-terminal fragment of the protein with an exposed destabilized N-terminal residue, preferably a destabilizing Ile, Glu, His, Tyr, Gln, Asp, Asn, Phe, Leu Trp, Lys, Arg, Ala, Ser, Thr or Cys, more preferably a destabilizing Type I residue selected from Glu, Gln, Cys, Arg, Lys and His. Preferably, the fragment is the product of a specific proteolytic cleavage at a site between residues 150-160 of aprataxin which also forms a 16.5-18 kDa N-terminal fragment.
- Activated fragments of synaptotagmin-like protein include a C-terminal fragment of the protein with an exposed destabilized N-terminal residue, preferably a destabilizing Ile, Glu, His, Tyr, Gln, Asp, Asn, Phe, Leu Trp, Lys, Arg, Ala, Ser, Thr or Cys, more preferably a destabilizing Type II residue selected from Leu, Ile, Tyr, Phe and Trp. Preferably, the fragment is the product of a specific proteolytic cleavage at a site between residues 1-50 which forms a 0.5-5 kDa N-terminal fragment.
- Activated fragments of MAPT (tau) include a 15-20 kDa fragment of the protein with an exposed destabilized N-terminal residue, preferably a destabilizing Ile, Glu, His, Tyr, Gln, Asp, Asn, Phe, Leu Trp, Lys, Arg, Ala, Ser, Thr or Cys, more preferably a destabilizing Type I residue selected from Glu, Gln, Cys, Arg, Lys and His. The fragment is the product of multi-site proteolytic cleavages.
- Activated fragments of cdc6 include two protein fragments starting with exposed destabilized N-terminal residues, preferably destabilizing Ile, Glu, His, Tyr, Gln, Asp, Asn, Phe, Leu Trp, Lys, Arg, Ala, Ser, Thr or Cys, more preferably destabilizing Type I residues selected from Glu, Gln, Cys, Arg, Lys and His. The fragments are the product of multi-site proteolytic cleavages. One of the activated fragments is a peptide with a molecular weight of 40-45 kDa.

Therefore, the use of variants of proteins according to the claimed invention is described throughout the specification in a sufficient detail to satisfy the requirements of

the first paragraph of Section 112 (see M.P.E.P. § 2163.02, "Standard for Determining Compliance with the Written Description Requirement"). When one considers the high level of skill in the art, the skilled artisan would readily appreciate that Applicants have provided sufficient details regarding the parent polypeptides and proteins, their biological activities, sequences, and how to prepare variants thereof to use such molecules in the claimed invention. The Applicants have provided sufficient detail and defining characteristics for the claimed features to distinguish the invention. In addition, excerpts from the specification are provided above in the discussion regarding the Section 112, second paragraph, rejection that detail the variants used in the claimed invention.

Applicants have defined a product and methods that are broadly applicable to any of the proteins identified in the claims and variants thereof that includes the basic structural characteristics set forth in the claims. A variety of proteins are recited and their full sequences are provided. Further defined is what is intended by variants of these sequences, including those primary destabilizing N-terminal residues within these proteins. This is sufficient disclosure of the basic structural features to enable the skilled artisan can clearly envision the members of the genus of compounds encompassed by the claims. The skilled artisan can also envision that genus and the species that fall within. Therefore, it is clear that Applicants were in possession of the claimed invention.

Second, the Examiner alleged on page 3 of the Office Action, "The formation of a conjugate by N-end rule ubiquitylation does not sufficiently describe the conjugate structure because the enzymes involved in forming the conjugates are unknown and it is not clearly described as to how the conjugation occurs between the two molecules."

Again, Applicants disagree. The final structure of the ubiquitylated conjugate is clear from requiring "N-end rule ubiquitylation of a polypeptide comprising a destabilizing N-terminal residue plus an internal Lys residue" according to the claims. In paragraph [0008], they teach how the conjugate is formed:

> One specific example of an important ubiquitylation pathway is N-End rule ubiquitylation, and especially N-End rule ubiquitylation where ubiquitylation is preceded by N-terminal segment cleavage, where the N-terminal segment comprises one or more amino acid residues. The proteolysis exposes an N-degron which comprises a destabilizing N-terminal residue plus an internal Lys residue where a multi-Ub chain is later attached. The

> N-terminal segment is cleaved to form an activated substrate of the Ub-dependent N-end rule pathway (activated fragment) which is recognized through exposed destabilizing N-terminal residue.

Therefore, the final structure of the ubiquitylated conjugate is ubiquitin chain(s) attached to the internal Lys residue of the substrate. The segment to the N-terminus of the Lys residue is cleaved from the rest of the substrate.

The inquiry into whether the description requirement is met must be determined on a case-by-case basis and is a question of fact. *In re Wertheim*, 541 F.2d 257, 262, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976). A discloscue as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. **The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims.** *Wertheim*, 541 F.2d at 263, 191 U.S.P.Q. at 97. [M.P.E.P. § 2163.04, emphasis added]

In view of this portion of the M.P.E.P., the Examiner has not met his burden of proof. He objects to the breadth of the pending claims without considering whether that breadth is supported by Applicants' specification in context: i.e., would one skilled in the art recognize in the instant disclosure a description of the invention defined by the claims? Contrary to Examiner's assertions, the present specification provides extensive disclosure of the proteins and variants thereof. Still further, the level of skill in the art is high, such that given the extensive disclosure in the specification, the skilled artisan would readily appreciate metes and bounds of the instant invention, and readily envisage the species within the claimed genus and the structure of the final product.

Still further, M.P.E.P. § 2163 III-3(a) clearly states that although structural formulas provide a convenient method of demonstrating possession of specific molecules, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession. As explained by the Federal Circuit, "there is no per se rule that an adequate written description of an invention that involves a biological

macromolecule must contain a recitation of known structure." *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 U.S.P.Q.2d 1001, 1007 (Fed. Cir. 2006). See also *Capon v. Eshhar*, 418 F.3d at 1358, 76 U.S.P.Q.2d at 1084 ("The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes" where the genes were novel combinations of known DNA segments.). For example, a disclosure of unique cleavage by particular enzymes, isoelectric points of fragments, detailed restriction enzyme maps, a comparison of enzymatic activities, or antibody cross-reactivity may be sufficient to show possession of the claimed invention to one of skill in the art. See *Lockwood*, 107 F.3d at 1572, 41 U.S.P.Q.2d at 1966 ("written description" requirement may be satisfied by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention").

Withdrawal of the written description rejection made under Section 112, first paragraph, is requested because the specification conveys to a person skilled in the art that Applicants were in possession of the claimed invention as of the filing date.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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